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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,395	09/06/2001	Duncan Robert Armour	PG3612USW	8883

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DAVID J LEVY, CORPORATE INTELLECTUAL PROPERTY
GLAXOSMITHKLINE
FIVE MOORE DR., PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,395	ARMOUR ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-55* is/are pending in the application.

4a) Of the above claim(s) *49-55* is/are withdrawn from consideration.

5)☒ Claim(s) *29-43 and 48* is/are allowed.

6)☒ Claim(s) *44-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of Group 1 without traverse is acknowledged. Claims 29-55 remain pending. Claims 45-48 are now rejoined with the elected group. Claims 29-48 are examined in this Office action.

It is suggested that claims 49-55 be cancelled.

*

35 U.S.C §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 47 is rejected under 35 USC §101 because the claimed invention is not supported by a well-established utility.

Claim 47 asserts that "prophylaxis" of inflammatory diseases can be achieved by administering one of the claimed compounds. As it happens, there is no evidence that a disease can be "treated", but if, at some point in the future, applicants provide evidence that a disease can be successfully treated, this ground of rejection will be maintained because of the term "prophylaxis". This term is interpreted to encompass an assertion of outright prevention. "Prevention" means that not a single test subject will develop any symptoms of a disease. For example, suppose that one of the claimed compounds were administered to each of 1000 human subjects over a period of six months, and that during the 6 months, 999 of the subjects were completely and totally healthy by any diagnostic measure. But suppose that of the 1000 subjects, one caught a minor cold (leading to

rhinitis, one of the recited disorders), from which he recovered after a few days. Such an experiment would be considered successful by almost any standard, but insofar as "prophylaxis" is concerned, the result with the one patient who caught a cold would actually constitute evidence of failure. The "bar" to overcome in demonstrating prevention is qxuite high, and not even a first step towards this goal has been undertaken.

It is suggested that the term "prophylaxis" be deleted from claim 47.

Claim 47 is also rejected under 35 USC. §112 first paragraph. Specifically, since the claimed invention is not supported by a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that representative compounds of the invention can antagonize VLA-4. Also shown (page 70) is that, using the assay described on page 18, eosinophil

accumulation in the lungs of guineau pigs could be reduced. Also asserted (page 70, line 8) is that if the compound is given 30 minutes prior to antigen challenge, an unidentified "hyper-reactivity" parameter can be reduced. Exactly what this "hyper-reactivity" parameter refers to is not made clear. Nor is it clear how the determination of this "hyper-reactivity" parameter is to be reconciled with the use of mepyramine. Given the nebulous nature of the experiments, it is not evident that enablement exists for treatment of asthma, or for treatment of any other respiratory disorder. Perhaps reducing eosinophil accumulation in lungs is better than not reducing it. But reducing eosinophil accumulation does not amount to a successful treatment of any of the recited diseases. And supposing that, at some point in the future, applicants can demonstrate actual reduction of airway hyperresponsiveness or some other process that would be of benefit to asthma sufferers, this would still not enable a claim drawn to treatment of asthma, for each of at least two reasons. Consider the following references:

- Foster, P. S. (*Clinical and Experimental Allergy* **29** (1) 12-6, 1999) discloses (page 13, col 1) that anti-IL-4 mAb's are effective in attenuating airway hyperresponsiveness if administered during the primary sensitization phase, but not during the period or direct provocation of the airways with allergen. This raises the issue of the timing of administration of the potentially "active agent", and raises the possibility that, even if the claimed compounds are effective to inhibit bronchoconstriction if administered before allergen challenge, they might not be effective if administered after symptoms of bronchoconstriction had already developed. The claims encompass both possibilities.

- Henderson (*J. Immunol.* **164**, 1086-95, 2000) discloses that administration of soluble IL-4 receptor (sIL-4R) prior to OVA challenge inhibited the inflammatory response, but only if administered intranasally. If administered i.p., the sIL-4R was not effective. This raises the possibility that even if the claimed compounds are effective to inhibit bronchoconstriction if administered directly to the lung, they might not be effective if adminstered orally. The claims encompass both possibilities.

Neither of the foregoing (Foster or Henderson) discusses VLA-4 specifically. But the point of the Foster reference is that even if it should turn out, at some point in the future, that the claimed compounds can inhibit bronchoconstriction if administered before allergen challenge, this will not prove that the compounds will be be effective if administered after symptoms of bronchoconstriction had already developed. A claim which is drawn to treatment of asthma by administering a compound after symptoms of bronchoconstriction had already developed would not be enabled. The Henderson reference is concerned with the relationship between efficacy and route of administration.

Currently, no claim is drawn to pulmonary administration of the compound. Accordingly, if a claim were to be added which is drawn to treatment of asthma by oral or parenteral administration, such a claim would be justifiably rejected for lack of enablement.

Applicants are asserting (p. 20, line 14+) that the compounds will be effective in the treatment of diseases of the respiratory tract, bronchitis, chronic bronchitis, asthma, allergen-induced asthmatic reactions, chronic obstructive pulmonary disease (COPD),

diseases of the GI tract, intestinal inflammatory diseases, inflammatory bowel disease, Crohn's disease, ulcerative colitis, intestinal inflammatory diseases secondary to radiation exposure or allergen exposure, rhinitis, nephritis, skin diseases, psoriasis, allergic dermatitis, hypersensitivity reactions, diseases of the central nervous system which have an inflammatory component, Alzheimer's disease, meningitis, multiple sclerosis, AIDS dementia, atherosclerosis, peripheral vascular disease, idiopathic hypereosinophilic syndrome, auto-immune diseases, allograft tissue rejection, rheumatoid arthritis, and diabetes. However, it is not the case that treatment of any of these diseases is enabled.

While it may be true that $\alpha 4\beta 1$ integrins are peripherally involved in each of these disease states, it is far from clear that a disorder in the binding of integrins is the primary cause of the diseases. In addition, it is not established that the compounds, if administered, will reach the appropriate anatomical site(s), that they will accumulate to a sufficient extent to be effective

The assertion by the examiner is that (a) structure/activity relationships in VLA-4 antagonism are unpredictable, and (b) treatment of inflammatory conditions is unpredictable as well. Consider the following:

- Dutta (*Journal of Peptide Science* **6**, 321-341, 2000) has examined the efficacy of various peptides in the antagonism of VLA-4/VCAM-1 binding. As stated on page 329, col 2, last two lines, the following two compounds were inactive both *in vitro* and *in vivo*:

  cyclo[Ile-Leu-Asp-Val-NH $(CH2)_2CO$]
  Ac-cyclo(Orn-Leu-Asp-Val)

These peptides are minor variations of peptides that were active.

- Arrhenius (*USP 5,688,913*) discloses (cols 17-18) several examples of compounds which failed to antagonize VLA-4. These compounds are minor variations of other compounds that were potent antagonists of VLA-4.

- Komoriya, Akira (*J. Biol. Chem.* **266** (23), 15075-15079, 1991) discloses that in an assay of $\alpha_4\beta_1$ activity, the pentapeptide EILEV was active, but pentapeptide EILDV was not. This latter peptide differs from the former by just one methylene unit.

- Haworth, Duncan (*Br. J. Pharmacol.* **126**(8), 1751-1760, 1999) discloses various VLA-4 antagonists. At least one of the disclosed compounds was inactive; this compound differed by only a few methylene units from a compound that was active.

- Haubner (*J. Am. Chem. Soc.* **118**, 7881, 1996) discloses (table 2) two compounds which failed to inhibit fibrinogen binding to the $\alpha_{IIb}\beta_1$ receptor, and vitronectin binding to the the $\alpha_V\beta_3$ receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity. These data argue for "unpredictability" in structure activity relationships of integrins generally. In addition, the "unpredictability" in structure activity relationships of RGD-peptides has direct relevance to the claimed compounds. As disclosed in Yang Y (*European Journal of Immunology* **28** (3) 995-1004, 1998) RGD-containing peptides can bind to VLA-4. Thus, if one cannot predict structure activity relationships of RGD peptides in their binding to VLA-4, it stands to reason that such unpredictability extends to other compounds which either do bind VLA-4, or which are asserted to exhibit such an effect.

In addition to the foregoing, the following references teach "failure" in the treatment of one or more inflammatory conditions:

Vatistas N J, "Infection of the intertubercular bursa in horses: four cases (1978-1991)", [*Journal of the American Veterinary Medical Association* **208** (9) 1434-7, 1996];

Tait A, "Synthesis and antiinflammatory activity of 2,6-bis(1,1- dimethylethyl) phenol derivatives" (*Farmaco* **48** (10) 1463-73, 1993);

Kurokawa M "Synthesis and antiinflammatory activity of cis- and trans- 6,6a, 7,8,9,10,10a,11- octahydro-11-oxodibenzo[b,e]thiepinacetic and -oxepinacetic acids" (*Journal of Medicinal Chemistry* **33** (2) 504-9, 1990);

Uren M F, "The effect of anti-inflammatory agents on the clinical expression of bovine ephemeral fever" (*Veterinary Microbiology* **19** (2) 99-111, 1989;

Crossley M J, "Studies on the effects of pharmacological agents on antigen-induced arthritis in BALB/c mice" (*Drugs Under Experimental and Clinical Research* **13** (5) 273-7, 1987).

Thus, structure/activity relationships involving VLA-4 are unpredictable. Applicants may be able to point to one or more compounds from the prior art which are effective to treat one or more of the recited diseases. However, as is clear, the efficacy in vitro occurs over a broad range, and one cannot compare the effects of the claimed compounds with other (prior art) compounds. No correlation has been established between the in vitro data, and successful treatment of any of the foregoing diseases. Moreover, other issues such as bioavailability and pharmacokinetics are not reflected in this in vitro data.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As is evident, extrapolation from

an observation of VLA-4 binding in vitro to treatment of the various recited diseases will produce "unpredictable" results.

In addition to the foregoing, consider the following:

- Pierce, J. W., ("Salicylates inhibit I kappa B-alpha phosphorylation, endothelial-leukocyte adhesion molecule expression, and neutrophil transmigration", Journal of Immunology, 156 (10) 3961-9, 1996) discloses that aspirin inhibits ICAM-1 and VCAM-1 expression. In a similar vein, Gonzalez-Alvaro I ("Interference of nonsteroidal antiinflammatory drugs with very late activation antigen 4/vascular cells adhesion molecule 1-mediated lymphocyte-endothelial cell adhesion", Arthritis and Rheumatism 41 (9) 1677-88, 1998) discloses that indomethacin inhibits VLA-4/VCAM-1 interactions. If applicants' assertions were correct, the skilled artisan would predict that success in the treatment of inflammatory conditions would be achieved by any compound which antagonizes VLA-4/VCAM-1 interactions. Yet this is not what one finds. For example, Goldenberg M M ("A pharmacologic analysis of the action of platelet-activating factor in the induction of hindpaw edema in the rat", Prostaglandins 28 (2) 271-8, 1984) discloses that neither indomethacin nor aspirin was effective to inhibit an inflammatory response to paw edema in rats. Similarly, Zuany-Amorim C. (European Journal of Pharmacology 257 (3) 211-6, 1994), discloses that aspirin failed to inhibit inflammatory responses to antigen (e.g., page 214, col 1). These findings of Goldenberg and of Zuany-Amorim support the examiner's contention that one cannot predict success in the treatment of inflammatory diseases merely because one can antagonize VLA-4/VCAM-1 interactions in vitro. As two more examples, Rordorf C "Arthritis in MRL/LPR mice and in collagen II sensitized DBA-1 mice and their use in pharmacology", International Journal of Tissue Reactions 9 (4) 341-7, 1987 discloses that indomethacin was not effective to treat arthritis in an animal model, and Goldlust M B (Agents and Actions 11 (6-7) 729-35, 1981) discloses that aspirin was not effective to treat synovitis in rabbits.

- Theien, B. E. (*Journal of Clinical Investigation* **107** (8) 995-1006, 2001) compared the ability of anti-VLA-4 to regulate proteolipid protein (PLP) 139-151-induced R-EAE when administered either before or after disease onset. Preclinical administration of anti-VLA-4 either to naive recipients of primed encephalitogenic T

cells or to mice 1 week after peptide priming, i.e., before clinical disease onset, inhibited the onset and severity of clinical disease. In contrast, Ab treatment either at the peak of acute disease or during remission exacerbated disease relapses and increased the accumulation of CD4(+) T cells in the CNS. Most significantly, anti-VLA-4 treatment either before or during ongoing R-EAE enhanced Th1 responses to both the priming peptide and endogenous myelin epitopes released secondary to acute tissue damage. Collectively, these results suggest that treatment with anti-VLA-4 Ab may be problematic in treating established autoimmune diseases such as MS. Accordingly, one cannot predict success in the treatment of MS based on the propensity of a compound to antagonize VLA-4.

- Saez-Torres I ("Peptide T does not ameliorate experimental autoimmune encephalomyelitis (EAE) in Lewis rats", *Clinical and Experimental Immunology* **121** (1) 151-6, 2000) discloses that it is known in the art that peptide T inhibits T cell activation and cytokine production and function. Saez-Torres studied the ability of peptide T to ameliorate EAE in Lewis rats. Peptide T was administered subcutaneously at different doses and phases of the disease according to several treatment protocols. The authors concluded that peptide T neither prevents nor ameliorates EAE in Lewis rats. This supports the conclusion that one cannot "predict" success in the treatment of inflammatory conditions, even if one is able to inhibit T cell activation and cytokine production. This finding of Saez-Torres is relevant in part because VLA-4 is prominently expressed on circulating T-cells.

The foregoing teachings further support the conclusion that one cannot predict efficacy in the treatment of human disease merely by modulating *alpha* 4/ligand interactions *in vitro*. Clearly, "undue experimentation" would be required to practice the claimed invention. It is suggested that the term "pharmaceutical" be deleted from each of claims 44-46, and that claim 47 be cancelled. If deemed appropriate, a claim can be added which recites a method of antagonizing VLA-4. The following claim can also be added if deemed appropriate:

A method of inhibiting eosinophil infiltration into the lungs of a patient comprising administering an effective amount of a compound of claim 1 to a patient in need thereof.

*

Claims 45 - 47 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 46 recites the following phrase: "for use as a pharmaceutical". However, this renders the claim indefinite as to objectives.

- In claim 47, the phrase "for example, asthma" fails to set the metes and bounds. In the event that applicants can, at some point in the future, provide evidence that treatment of asthma (by pulmonary administration) is enabled, it will be suggested that a claim drawn to treatment of the same be added.

- Claim 45 recites the phrase "in combination together". However, this appears to be redundant.

- Claim 47 is indefinite as to the objectives of the treatment, and to the manifestations of a successful treatment. This rejection applies regardless of what diseases may be encompassed. For asthma in particular, the claim is indefinite as to the manifestations of a successful treatment. For example, would applicants regard a reduction in the eosinophil count as constituting a successful treatment, or must there be a mitigation of bronchoconstriction...?

*

The following two articles have been cited on the PTO-892. These articles are referred to on page 18 of the specification:

Danahay H (*British journal of pharmacology* 120 (2) 289-97, 1997)

Sanjar (*Am Rev Respir Dis* 145, A40, 1992)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1600